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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JOYCE, CATHERINE	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/738,404	THORPE ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-12,25,29-31,34-39,41,42,46 and 47* is/are pending in the application.

4a) Of the above claim(s) *36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-12,25,29-31,34,35,41,42,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Claims 3-12, 25, 29-31, 34-39, 41, 42, 46 and 47 are pending, and claims 36-39 are withdrawn from consideration as being drawn to a non-elected invention.

2. Claims 3-12, 25, 29-31, 34, 35, 41, 42, 46 and 47 are under examination.

3. Applicant's election with traverse of Group II in the reply filed on November 29, 2005 is acknowledged. The restriction requirement between the inventions of Group I and Group II is withdrawn and the inventions of both groups I and II are under examination. It is noted that the Restriction Requirement mailed November 2, 2005 contained a typographical error in that an election of species requirement was not set forth. In a telephone call to Shelley Fussey on February 16, 2006, Examiner Catherine Joyce set forth a an election of species requirement as follows:

Claim 5 is generic to a plurality of disclosed patentably distinct species comprising methods of treating cancer. The species are as follows: (a) the first antibody of the immunoconjugate comprises a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 (claim 10); (b) the first antibody of the immunoconjugate comprises a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:9 (claim 10). The methods are patentably distinct because they are directed to the use of structurally distinct components.

Claim 31 is generic to a plurality of disclosed patentably distinct species comprising methods of treating cancer. The species are as follows: (a) a second anti-cancer agent is a chemotherapeutic agent; (b) a second anti-cancer agent is a radiotherapeutic agent; (c) a second anti-cancer agent is an anti-angiogenic agent; (d) a second anti-cancer agent is an apoptosis-inducing agent; (e) a second anti-cancer agent is a steroid; (f) a second anti-cancer agent is an antimetabolite; (g) a second anti-cancer agent is an anthracycline; (h) a second

anti-cancer agent is a vinca alkaloid; (i) a second anti-cancer agent is an antibiotic; (j) a second anti-cancer agent is a cytokine; (k) a second anti-cancer agent is an alkylating agent; (l) a second anti-cancer agent is a coagulant; (m) a second anti-cancer agent is an anti-tubulin drug (all in claim 34). Claim 35 will be examined only to the extent it reads on the elected species. The methods are patentably distinct because they are directed to the use of structurally distinct components.

In response to the election of species requirement, Shelley Fussey elected the species wherein the first antibody of the immunoconjugate comprises a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 and the species wherein the second anti-cancer agent is a chemotherapeutic agent. Thus claims 36-39 are withdrawn from consideration as being drawn to a non-elected invention, and claim 35 will be examined to the extent it reads on chemotherapeutic agents, i.e. colchicines, taxol, vinblastine, vincristine, and vindescine. Affirmation of this election of species requirement is required in the response to this Office Action.

Specification

4. The specification on page 1 should be amended to reflect the status of the parent application serial number 09/561,005.

Priority

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the

invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/508,251, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Particularly claims 3-12, 25, 29-31, 34, 35, 41, 42, 46 and 47 are not supported by the prior-filed application because the disclosure of a method for treating cancer comprising administering to an animal (i) a first immunoconjugate that comprises a cleavage agent or enzyme operatively attached to at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof that binds to substantially the same epitope as the monoclonal antibody 2C3 and (ii) subsequently administering to the animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to the antibody, thereby releasing a substantially active drug specifically within the vasculature or stroma of the tumor is not found in the prior filed application. Further, the particular operatively matched cleavage agent or enzyme and inactive prodrugs of claim 41 are not found in the prior filed application. See MPEP § 2163 - § 2163.07(b) for a discussion of the written description requirement of 35 U.S.C. 112, first paragraph. Thus claims 3-12, 25, 29-31, 34-39, 41, 42, 46 and 47 are hereby assigned the priority date of April 28, 2000, the filing date of the instant Application. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date of April 28, 2000 for the instantly claimed application serial number 10/738404, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is indefinite because claim 9 recites the phrase a "chimeric antibody". The exact meaning of the word chimeric is not known. The term chimeric is generic to a class of antibodies which are products of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies.

Claims 3-12, 25, 29-31, 34, 35, 41, 42, 46 and 47 are indefinite because claims 5 and 46 recites the phrases "substantially inactive prodrug" and "substantially active drug". The cited terms are relative term which render the claims indefinite. The cited terms are not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating cancer comprising administering to animal a substantially inactive prodrug and a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen binding antibody fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3, wherein the immunoconjugates comprises variable regions that include the amino acid sequences of SEQ ID NO:7 or SEQ ID NO:9, does not reasonably provide enablement for a method for treating cancer comprising administering to animal a substantially inactive prodrug and a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antibody fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3, wherein the immunoconjugates comprises variable regions that include the amino acid sequences of SEQ ID NO:7 or SEQ ID NO:9

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art,

(7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claim is drawn to a method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of (a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), thereby localizing the immunoconjugate to the vasculature or stroma of said vascularized solid tumor, and (b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor, wherein said at least first antibody of said immunoconjugate comprises at least a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9 (claim 10).

The specification teaches an anti-VEGF antibody (2C3) that specifically inhibits VEGF binding to the VEGR2 receptor, that has significant anti-tumor effects in-vivo, and that does not inhibit VEGF binding to the VEGFR1 receptor. The specification further teaches that the sequences of SEQ ID NO:7 and SEQ ID NO:9 are the sequences of Vh (variable region of the heavy chain) and Vκ (variable region of the light chain), encompassing CDR1-3 (complementarity determining regions) of the variable regions of the heavy and light chains (page 21, lines 22-29) of the 2C3 antibody (page 21, lines 22-29).

The teaching of the specification cannot be reasonably extrapolated to the scope of the claims because one of skill in the art could not predict that a

functional antibody the comprises the Vh region of the 2C3 antibody without the Vκ region, or the Vκ of the 2C3 antibody without the Vh region, (i.e. an antibody that comprises SEQ ID NO:7 or SEQ ID NO:9) could be made or that it would bind to substantially the same epitope as the monoclonal antibody 2C3. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs, in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Thus, it is unlikely that antibodies which comprise less than the full complement of CDRs from the heavy and light chain variable regions of the 2C3 antibody can be made or will function as claimed. The specification provides no direction or guidance regarding how to produce antibodies having the recited binding capabililty wherein the antibodies comprise Vh region of the 2C3 antibody without the Vκ region, or the Vκ of the 2C3 antibody without the Vh region. Therefore, in view of the lack of guidance in the specification on making functional antibodies that comprise the Vh region of the 2C3 antibody without the Vκ region, or the Vκ of the 2C3 antibody without the Vh region, and the teaching in the art that the

formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, it cannot be predicted that functional antibodies having the recited structure can be made. Therefore, undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any

inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 3-6, 8, 9, 11, 12, 25, 41, 42 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brekken et al. (1998, Cancer Research 58:1952-1959) in view of Melton et al. (1996, J. of the National Cancer Institute 88(3/4):153-165) and Presta et al. (1997, Cancer Res. 57(20):4593-9) (abstract).

The claims are drawn to the following: a method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of (a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), thereby localizing the immunoconjugate to the vasculature or stroma of said vascularized solid tumor, and (b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor (claim 5),

wherein said immunoconjugate binds to VEGF bound to the VEGF receptor VEGFR1 expressed by endothelial cells of the vasculature of said vascularized tumor (claim 3),

wherein said immunoconjugate binds VEGF bound within the stroma of said vascularized tumor (claim 4),

wherein at least a first antibody of said immunoconjugate is a monoclonal antibody or an antigen-binding fragment thereof (claim 6),

wherein said at least first antibody of said immunoconjugate is a human, humanized or part-human antibody or antigen-binding fragment thereof (claim 8),

wherein said at least first antibody of said immunoconjugate is a chimeric antibody or a recombinant antibody (claim 9),

wherein said at least first antibody of said immunoconjugate is the monoclonal antibody 2C3(ATCC PTA 1595) (claim 11),

wherein said at least first antibody is operatively attached to two or more cleavage agents or enzymes (claim 12)

wherein said immunoconjugate comprises the at least a first antibody operatively attached to the at least a first cleavage agent or enzyme as fusion protein prepared by expressing a recombinant vector that comprises, in the same reading frame, a DNA segment encoding the antibody operatively linked to a DNA segment encoding the cleavage agent or enzyme (claim 25),

wherein said at least a first cleavage agent or enzyme and said at least one substantially inactive prodrug are operably matched agents selected from the groups consisting of: (a) alkaline phosphatase, arylsulfatase, serratia protease, thermolysin, subtilisin, a carboxypeptidase, a cathepsin, D-alanylcarboxypeptidase, .beta.-galactosidase, neuramimidase, .beta.-lactamase, penicillin amidase and cytosine deaminase; and (b) a phosphate-containing prodrug, sulfate-containing prodrug, peptide-based prodrug, D-amino acid-modified prodrug, glycosylated prodrug, .beta.-lactam-containing prodrug, optionally substituted phenoxyacetamide- or phenylacetamide-containing prodrug and 5-fluorocytosine (claim 41),

wherein said animal is a human patient (claim 42),

and

a method for treating cancer, comprising administering to an animal that has a vascularized solid tumor: (a) a first composition comprising at least a first

immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that effectively competes with the monoclonal antibody 2C3 (ATCC PTA 1595) for binding to VEGF, thereby localizing said immunoconjugate to the vasculature or stroma of said vascularized solid tumor; and (b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor (claim 46).

Brekken et al. teaches anti-VEGF antibody (2C3) that blocks the interaction between VEGF and the VEGF receptor KDR/Flk-1, that inhibits VEGF-mediated growth of endothelial cells in vitro, and that localizes strongly to connective tissue in tumors after injection into mice bearing human tumor xenografts (abstract). Brekken also teaches that biotinylated 2C3 produced intense staining of connective tissue surrounding the vasculature of the H358 human NSCLC tumor after i.v. injection, with large tracks of stromal tissue that connect the tumor cell nests being stained with 2C3 and the most intense localization being observed in the largest tracks of stroma (page 1956). Brekken also teaches that endothelial cells in vessels not surrounded by stroma, such as vessels running through nest of tumor cells themselves were stained in some cases (page 1956). Brekken also teaches that 2C3 is potentially a vehicle for targeting therapeutic agents to tumor connective tissue (1958).

Brekken teaches as set for above but does not specifically teach a method of treating cancer comprising administering an anti-VEGF antibody having a cleavage agent or enzyme operatively attached and administering an inactive prodrug that is cleaved by the cleavage agent or enzyme thereby releasing a substantially active drug specifically within the vasculature or stroma of the tumor.

Presta et al. teaches that a murine anti-human VEGF monoclonal antibody A.4.6.1 has been shown to potently suppress angiogenesis and growth in a variety of human tumor cell lines transplanted into nude mice and that a humanized version of the antibody inhibits VEGF-induced proliferation of endothelial cells in vitro and tumor growth in vivo with potency and efficacy very similar to those of the murine antibody (abstract). Presta suggests that inhibition of VEGF-induced angiogenesis with an anti-VEGF antibody is a valid strategy for the treatment of solid tumors in humans (abstract)

Melton teaches that the use of antibody-enzyme conjugates directed at tumor-associated antigens to achieve site-specific activation of prodrugs to potent cytotoxic species, termed "antibody-directed enzyme prodrug therapy" (ADEPT), has a particular advantage in that it may allow the use of potent agents that are too toxic to be used in conventional chemotherapy (abstract). Melton also teaches that the ADEPT system offers the potential to overcome problems associated with drug or toxin immunoconjugates including that such as lack of expression of a target antigen on all tumor cells and the fact that antibodies penetrate tumors poorly (page 153, second column thru page 154, first column). Melton also teaches fusion proteins comprising both antigen-binding and enzymatic activities and humanized antibodies (abstract). Melton also teaches that the enzyme/prodrug systems may comprise carboxypeptidase G2, carboxypeptidase G2, carboxypeptidase A, alkaline phosphatase, penicillin amidase, β-glucuronidase, β-lactamase, and cytosine deaminase and associated substrates (Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the anti-VEGF tumor targeting 2C3 antibody of Brekken in the VEGF-targeted antibody immunotherpay methods for the treatment of tumors as described by Presta and to employ the antibody-directed enzyme prodrug therapy of Melton in conjunction with the 2C3 antibody. One of ordinary skill in the art would have been motivated to substitute the

antibody of Brekken for the antibody described by Presta because of the teaching in Brekken that the 2C3 antibody localizes strongly to tumors. One of ordinary skill in the art would have been motivated to employ the ADEPT system in conjunction with the 2C3 antibody because Melton teaches the advantages of using the ADEPT system for antibody based tumor targeting. One of skill in the art would have had a reasonable expectation of success in making the substitution of the 2C3 antibody in the treatment method of Presta and in using the ADEPT system in conjunction with the 2C3 antibody because of the stated success in Presta of anti-VEGF antibodies in inhibiting tumor growth, the teaching in Brekken that the anti-VEGF 2C3 antibody localizes strongly to tumors, and the stated success in Melton of using the ADEPT system with tumor immunotherapy. One of skill in the art would have been motivated to attach two or more cleavage agents or enzymes to the antibody, and would have had a reasonable expectation of success in doing so, because of the advantages that could be expected from multiple cleavage agent or enzyme attachments in terms of efficiency of enzyme or cleavage agent conversion of the prodrug. That is, a higher concentration of cleavage agents or enzymes at the tumor target site would be expected to generate a greater local concentration of active drug and therefore result in enhanced anti-tumor activity.

10. Claims 5, 7, 29-31, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brekken et al. (1998, Cancer Research 58:1952-1959) in view of Presta et al. (1997, Cancer Res. 57(20):4593-9) (abstract) and Melton et al. (1996, J. of the National Cancer Institute 88(3/4):153-165), and further in view of US Patent No. 5,863,538 and US Patent No. 5,621,002.

The claims are drawn to the following: a method for treating cancer, comprising administering to an animal that has a vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a therapeutically effective amount of (a) a first pharmaceutical composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme

operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), thereby localizing the immunoconjugate to the vasculature or stroma of said vascularized solid tumor, and (b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first pharmaceutical composition, thereby releasing a substantially active drug specifically within the vasculature or stroma of said vascularized solid tumor (claim 5),

wherein said at least first antibody of said immunoconjugate is an scFV, Fv, Fab', Fab, diabody, linear antibody or $F(ab')_2$ antigen-binding fragment of an antibody (claim 7),

wherein said a first pharmaceutical composition is administered to said animal intravenously (claim 29),

further comprising subjecting the animal to radiotherapy (claim 30),

further comprising administering to the animal a therapeutically effective amount of at least a second anti-cancer agent (claim 31),

wherein said at east a second anti-cancer agent is a chemotherapeutic agent (claim 34).

wherein said at least a second anti-cancer agent is colchicine, taxol, vinblastine, vincristine, or vindescine, or tumor-targeted form thereof (claim 35),

Brekken, Presta, and Melton teach as set forth above but do not specifically teach the intravenous administration of the immunoconjugate, the use of antibody that is an scFV, Fv, Fab', Fab, diabody, linear antibody or $F(ab')_2$ antigen binding fragment of an antibody, or the further administration of radiotherapy or a second cancer agent that is a chemotherapeutic agent, or the administration of colchicines, taxol, vincristine, or vindescine as the second therapeutic agent.

US Patent No. 5,863,538 teaches that, for vascular targeted tumor therapies, including immunotherapy, target cells are directly accessible to intravenously administered therapeutic agents, permitting rapid localization to a high percentage of the injected dose (column 3, lines 17-20). US Patent No. 5,863,538 teaches that advantages will be realized through combination regimens wherein both the tumor vasculature and the tumor itself are targeted, and that combination regimens may thus include targeting of the tumor directly with either conventional antitumor therapy, such as with radiotherapy or chemotherapy (column 14, line 56 thru column 15, line 9). US Patent No. 5,863,538 teaches that anticancer agents that may be employed include a steroid, an antimetabolite, an anthracycline, a vinca alkaloid, an antibiotic, an alkylating agent or an epipodophyllotoxin, or a plant-, fungus- or bacteria-derived toxin (claims 15 and 16). Exemplary antineoplastic agents that have been investigated include doxorubicin, daunomycin, methotrexate, vinblastine (column 43, lines 65-67). US Patent 5,863,538 further teaches that antibodies may be univalent fragments such as Fab' or Fab (column 5, lines 2-7).

US Patent No. 5,621,002 teaches that pharmacologically active substances for use in anti-tumor therapy, particularly for use as prodrugs, include vindesine, vincristine, vinblastine, colchicine, and taxol

It would have been obvious to combine the teaching of Brekken and Melton on the use of the tumor vasculature targeted 2C3 antibody conjugated to an enzyme or cleavage agent in conjunction with a prodrug for tumor therapy with the teaching of US Patent No. 5,863,538 on the intravenous administration of immunoconjugates, on the use of tumor vasculature targeted antibody therapies in conjunction with other anti-cancer therapies such as radiotherapy or chemotherapy, and on use of antibody fragments because of the advantages taught by US Patent No. 5,863,538 on intravenous administration and on using tumor vasculature targeted immunotherapies in conjunction with other anti-tumor therapies and because of the teaching in US Patent No. 5,863,538 of the art

recognized equivalence of antibody and antibody fragments. One would have had a reasonable expectation of success because of the success demonstrated in US Patent No. 5,863,538.

Further, it would have obvious to combine the teaching of Brekken, Melton, and US Patent No. 5,863,538 on the use of antibody conjugate/prodrug therapy in combination with a second therapeutic agent with the teaching of US Patent No. 5,621,002 on vindesine, vincristine, vinblastine, colchicine, and taxol as chemotherapeutic agents. One would have had a reasonable expectation of success because of the known pharmacological activity of vindesine, vincristine, vinblastine, colchicine, and taxol as described in US Patent No. 5,621,002.

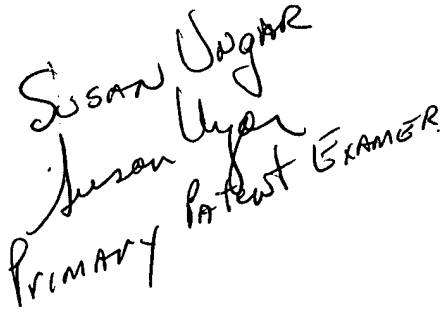
11. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Catherine Joyce
Examiner
Art Unit 1642